REMARKS

The Office Action mailed September 15, 2009, was reviewed and the comments of the Patent and Trademark Office were considered.

Claims 1 - 10, 13 - 22 and 24 were pending in the application. Claims 7, 8, 11, 12 and 23 have been canceled without prejudice. Claims 1, 3 - 6 and 17 have been amended by this response. Support for the amendments may be found at, for example, the original specification, such as paragraphs 0139 and 0146, and claims. Applicants respectfully submit that no new matter has been added by the amendments. Therefore, claims 1 - 6, 9 - 10, 13 - 22 and 24 are pending in the application and submitted for reconsideration.

Withdrawal of the rejections and allowance of all claims are respectfully requested.

Rejections under 35 U.S.C. § 112

Claims 1 - 10, 13 - 22, and 24 are rejected under 35 U.S.C. 112, second paragraph.

Claims 1 - 10, 13 - 22 and 24 are patentable under 35 U.S.C. 112, second paragraph because the subject matter is described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the invention was filed, had possession of the claimed invention.

The Examiner has rejected claims as allegedly failing to comply with the written description requirement because the claims are to a broad range of compounds. According to MPEP 2163(A), there is a strong presumption that an adequate written description of the claimed invention is present when the application is filed. Citing *In re Wertheim*, 541 F.2d 257, 263, 191 USPQ 90, 97 (CCPA 1976) ("we are of the opinion that the PTO has the initial burden of presenting evidence or reasons why persons skilled in the art would not recognize in the disclosure a description of the invention defined by the claims"). The MPEP also points out that the written description rejection for subject matter "of an original claim for lack of written description should be rare." MPEP 2163(II)(A).

First, the Examiner alleges that "the claims are drawn to a broad range of hydrophilic polymers and certain hydrophobic compounds [...]. However Applicant has provided very few examples" of very specific polymers in one ratio. *See* Office Action page 4. The Examiner

further alleges that the Applicant does not provide adequate description of "*a reasonable number of species within the claimed genus.*" *See* Office Action page 4.

As pointed out in MPEP 2163(II)(A)(3),

> As explained by the Federal Circuit, "(1) examples are not necessary to support the adequacy of a written description; (2) the written description standard may be met ... even where actual reduction to practice of an invention is absent; and (3) there is no per se rule that an adequate written description of an invention that involves a biological macromolecule must contain a recitation of known structure."

citing *Falkner v. Inglis*, 448 F.3d 1357, 1366, 79 USPQ2d 1001, 1007 (Fed. Cir. 2006).

Here there is not a broad range of hydrophilic polymers but, to the contrary, there are only a few, because:

1) they are hydrophilic polymers carrying groups that are ionized at neutral pH, and

2) they must be pharmaceutically acceptable.

As a consequence, those two conditions limit polymer A to pharmaceutically acceptable polymers having a free carboxylic function. Such polymers are well-known and have a well-characterized structure for one of skill in the art. In most embodiments that can be practiced, polymer A is restricted to (meth)acrylic (co)polymers and certain cellulose derivatives. Similarly, the number of compounds useful for compound B is limited (15 are listed in claim 1) and well-known such that one of skill in the art would know their structure. Given the disclosed teachings of the specification, there is a definite "correlation or relationship between the structure of the invention and its function." Given the examples and the teachings in the patent of the equivalence in function for these molecules, when formulated as described, withdrawal of the rejection is requested.

Indeed, compositions according to the invention made by the inventor after the application was filed demonstrate a definite relationship between the structure and function of the invention. Several representative compositions, a description of their formation, and figures showing their release profiles are discussed in the enclosed Preparation Declaration of Catherine Castan. ("Preparation Castan Declaration"). Compound 1 was formed with the active ingredient losartan, polymers A Eudragit L100-55 and Eudragit S100, and the hydrophobic compound Lubritab (hydrogenated cotton seed oil). Compound 2 was formed with the active ingredient

losartan, polymer A Eudragit L100-55, and the hydrophobic compound Lubritab (hydrogenated cotton seed oil). Compound 3 was formed with the active ingredient ramipril, polymer A hydroxypropylmethylcellulose phthalate (HPMCP) and the hydrophobic compound Lubritab (hydrogenated cotton seed oil). Compounds 1 – 3 have a B/A of 0.66.

Thus, all of these compounds have a similar structure: an active principle, one or more polymers A and a hydrophobic compound B. The specific active principles, specific polymers A, compounds B, and B/A ratio vary, yet all three compounds have similar properties. For instance, all compounds have the release profile claimed here: the release profile at a constant pH of 1.4 includes a latency phase with a duration less than or equal to 5 hours, and the change from pH 1.4 to pH 6.8, results in a release phase that starts without a latency period. These release profiles are clearly shown in Figure 1 – 3 of the Preparation Castan Declaration.

Applicants also remind the Examiner that the first paragraph of 35 USC §112 requires nothing more than objective enablement. Whether this is achieved by the use of illustrative examples or by broad terminology is of no importance. *In re Marzocchi*, 439 F.2d 220, 169 USPQ 367 (CCPA 1971). Further, there is a strong presumption that an adequate written description of the claimed invention is present when the application is filed. MPEP 2163.03.

The presence or absence of working examples should never be the sole reason for rejecting claims as being broader than the enabling disclosure. MPEP 2164.02; *see also, Ex parte Altermatt*, 183 USPQ 436 (POBA 1974); *Ex parte Kenaga*, 190 USPQ 346 (POBA 1974). As explained by the Court in *In re Robins*, 429 F2d 452, 166 USPQ 552 (CCPA 1970):

> Mention of representative compounds encompassed by generic claim language clearly is not required by sec. 112 or any other provision of the statute... Similarly, representative examples are not required by the statute and are not an end in themselves.

Thus, representative examples of each and every compound are not required under 35 U.S.C. § 112. Further, the Applicants include multiple working examples of the invention. *See*, specification at pages 16 – 17.

Examiner also relies on EP 1101490 ("Ishibashi") to assert that formulations that meet all of the characteristics of Applicant's formulations do not have the claimed behavior of two

mechanisms of release. *See,* Office Action at pages 5-6. Ishibashi has no bearing on the enablement of the claims because Ishibashi does not teach the claimed composition.

First, Ishibashi doesn't teach absorption in the upper parts of the gastrointestinal tract.

In Ishibashi, the objective of the invention is to avoid absorption in the upper parts of the GI tract, considered as a waste (see US 6,638,534: Column 1, lines 58-62), as the aim is to deliver locally in the large intestine anti-inflammatory agents to treat ulcerative colitis or Crohn's disease. The anti-inflammatory agents may be 5-amino salicylic acid (Fig. 1, 4, 5, 6) or sulfasalazine (Fig. 2 & 3). This is the opposite of the claimed invention where the aim is to have as much as possible of the active principle absorbed. The active principle is absorbed when it is in its absorption window, which, for the majority of active principles, is located in the upper part of the gastrointestinal tract (Claim 1).

Contrary to Ishibashi, the claimed invention intends to release the active principle in the stomach after a predetermined lag time (see release profile at pH 1.4). In addition, contrary to Ishibashi, the release at pH 6.8 starts immediately after the change of pH with no further lag time.

Ishibashi does not teach the claimed composition. The claimed composition has a specific particle size of between 200 and 800 µm. The compositions disclosed by Ishibashi all have a particle size greater than 930 µm. Ishibashi omitted the precise particle size in the examples, but the size of the particles is with certainty above 930 µm and most probably in the range of 1500 to 2500 µm. Here enclosed is the Ishibashi Declaration of Catherine Castan ("Ishibashi Castan Declaration") explaining how the particle size of Ishibashi is estimated from Ishibashi's disclosure.

The size of coated sustained-release particles is important and is directly linked to the observed result, i.e. the dissolution properties. The greater the particle size, the smaller the specific area. This means that the same amount of coating is applied on less surface area, thus, resulting in thicker coating and different release profiles. The coating takes more time to dissolve and can result in pronounced lag time at neutral pH.

In addition, although Ishibashi cites different types of hydrophobic compounds, it only discloses formulations containing stearic acid as a hydrophobic compound. Stearic acid is a

hydrophobic compound, but is also an acid, which has properties dependent on the pH. The behavior of stearic acid is different from that of other pure hydrophobic compounds without a pH sensitive moiety. The presence of the stearic acid product in the Ishibashi coating can also explain the different release profile. Fatty acids are not claimed in the present invention.

Therefore, claims 1 - 10, 13 - 22, and 24 are patentable under 35 U.S.C. 112, second paragraph. Withdrawal of the rejection and allowance of all claims are respectfully requested.

Double Patenting Rejections

Claims 1 - 10, 13 - 22 and 24 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1 and 12 - 41 of copending U.S. Application No. 10/996,780.

Claims 1 - 10, 13 - 22 and 24 are patentable copending U.S. Application No. 10/996,780. The cited reference cannot be used to reject the claims because the cited reference has a later priority date than the instant application.

The instant application claims priority to FR 01/122999, and thus has a priority date of October 9, 2001. In contrast, the cited application has a priority date later than the instant application. U.S. Application No. 10/996,780, filed November 24, 2004, has an earliest priority date of November 24, 2003.

Because this application has an earlier priority date, the cited application cannot represent prior art. As such, Applicants request the double patenting rejection be withdrawn.

Claims 1 - 10, 13 - 22 and 24 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1 and 18 - 23 of copending U.S. Application No. 11/449,675.

Claims 1 - 10, 13 - 22 and 24 are patentable copending U.S. Application No. 11/449,675. The cited reference cannot be used to reject the claims because the cited reference has a later priority date than the instant application.

The instant application claims priority to FR 01/122999, and thus has a priority date of October 9, 2001. In contrast, the cited application has a priority date later than the instant application. U.S. Application No. 11/449,675, filed June 9, 2006, has an earliest priority date of June 9, 2005.

Because this application has an earlier priority date, the cited application cannot represent prior art. As such, Applicants request the double patenting rejection be withdrawn.

Claims 1 - 10, 13 - 22 and 24 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 89 - 117 of copending U.S. Application No. 11/707,034.

Claims 1 - 10, 13 - 22 and 24 are patentable copending U.S. Application No. 11/707,034. The cited reference cannot be used to reject the claims because the cited reference has a later priority date than the instant application.

The instant application claims priority to FR 01/122999, and thus has a priority date of October 9, 2001. In contrast, the cited application has a priority date later than the instant application. U.S. Application No. 11/707,034, filed February 16, 2007, has an earliest priority date of June 15, 2005.

Because this application has an earlier priority date, the cited application cannot represent prior art. As such, Applicants request the double patenting rejection be withdrawn.

Claims 1 - 10, 13 - 22 and 24 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1 - 40 of copending U.S. Application No. 11/791,466.

Claims 1 - 10, 13 - 22 and 24 are patentable copending U.S. Application No. 11/791,466. The cited reference cannot be used to reject the claims because the cited reference has a later priority date than the instant application.

The instant application claims priority to FR 01/122999, and thus has a priority date of October 9, 2001. In contrast, the cited application has a priority date later than the instant application. U.S. Application No. 11/791,466, filed January 8, 2008, has the earliest priority date of November 24, 2004.

Because this application has an earlier priority date, the cited application cannot represent prior art. As such, Applicants request the double patenting rejection be withdrawn.

Rejections under 35 U.S.C. § 102

Claims 1, 2, 14, 15, 20 - 22 and 24 are rejected under 35 U.S.C. 102 (e) as being anticipated by Bartholomaeus et al. (U.S. Publication No. 2002/0176888), hereafter "Bartholomaeus".

Claims 1, 2, 14, 15, 20-22 and 24 are patentable over Bartholomaeus. Withdrawal of the rejection and allowance of all claims are respectfully requested.

Independent claim 1, as amended, requires: "wherein the weight ratio B/A is between 0.45 and 1.0".

Applicants respectfully disagree that Bartholomaeus discloses the claimed coating film comprising "at least one hydrophilic polymer A carrying groups that are ionized at neutral pH" and "at least one hydrophobic compound B is selected from the group consisting of hydrogenated palm oil, hydrogenated castor oil, hydrogenated soybean oil, glyceryl behenate, hydrogenated cottonseed oil, wax yellow, lanolin, anhydrous milk fat, hard fat suppository base, omega 3 fatty acids, lauroyl macrogolglycerides, glyceryl palmitostearate, cetyl alcohol, polyglyceryl diisostearate and glyceryl stearate".

The Office Action at page 10 cites paragraph 0036 of Bartholomaeus as "teaching mixtures of hydrophilic and hydrophobic material as retarding matrix material". Applicants point out that this statement is not supported by any example, nor does the description provide any demonstration of that statement either.

Above all, that statement is restricted to ***matrix*** formulations. Because Bartholomaeus clearly distinguishes between controlled-release matrix formulations and film-coated products

(Bartholomaeus at paragraph 0022), that statement can in no way be directed to film-coated formulations.

The Office Action cites to Example 1 as teaching a coating including "polymethacrylic acid methacrylate (equivalent to instantly claimed hydrophilic compound A) and glycerine monostearate (equivalent to instantly claimed hydrophobic compound B, glyceryl stearate)." Office Action at page 10. Even if Example 1 is assumed to cover compound A and compound B as claimed, neither the specification nor the examples teach that the weight ratio B/A is between 0.45 and 1.0.

In Example 1, the Office Action correlates glycerine monostearate to compound B as claimed and polymethacrylic acid methylmethacrylate to compound A. Polymethacrylic acid methylmethacrylate is present in the coating of Example 1 in the amount of 100.0 g. Glycerine monostearate is present in the coating of Example 1 in the amount of 1.8 g. Therefore, the weight ratio B/A as presented in Bartholomaeus is 0.018.

Bartholomaeus does not teach any higher ratios of compounds that correspond to the claimed hydrophilic compound A and hydrophobic compound B. The ratio of 0.018 taught in Bartholomaeus is not within or even similar to the claimed weight ratio of B/A between 0.45 and 1.0.

Regarding the release profiles at neutral pH and acidic pH, the Examiner states that the burden is upon the Applicant to prove that the product of Example 1 of Bartholomaeus and the claimed product do not have the same functional properties, in particular would yield different dissolution results at pH 1.4. The Office Action states "pH 1.2", but Applicants assume the Examiner meant pH 1.4 as claimed. Appropriate clarification is requested.

The release profiles obtained with formulations like Example 1 of Bartholomaeus and the profiles obtained with claimed formulations are different.

At neutral pH, the release of the active principle from formulations according to the claimed invention is quasi immediate and fast (see examples): within two hours at pH = 6.8, most (> 80 %) of the active principle is dissolved. In contrast, the dissolution in Example 1 of Bartholomaeus is very slow, extended over 18 hours, with only 25% of the active principle dissolved at 2 h (at pH = 7.2).

In Table 1 and Figure 1 of Bartholomaeus, there is no data point between 0 and 2 hours. The line segment drawn between the 0 and 2-hour data points is arbitrary; it is not possible to

exclude that a latency period does take place, whereas the release at that pH for the claimed product starts without a latency period.

The composition described in example 1 of Bartholomaeus is a large size pellet coated with Eudragit L30D, triethylcitrate and glycerine monostearate. Example 5 of Ishibashi (EP 1101490) shows that a very similar composition, i.e. a pellet of large size coated with Eudragit L100 (Eudragit L100 is the dry form of the suspension Eudragit L30D) and a fatty substance (compound B) shows similar results as compared to Ishibashi: at neutral pH, the release is slow, with a lag time (see figure 6 of Ishibashi) whereas the release at that pH for the claimed product is rapid and starts without a latency period.

Even more strikingly, Example 1 of Ishibashi (EP 1101490) shows that a large pellet coated with Eudragit L100 and stearic acid shows at pH = 1.2 no release for 10 hours, whereas the release at pH 1.4 for the claimed product starts after a latency period less than or equal to 5 hours.

All these examples show that, with a coating composed of a hydrophilic polymer carrying groups that are ionized at neutral pH and one hydrophobic compound, one can obtain very different release profiles and even opposite results. This is because the release profile is not only the consequence of the chemical nature of the components of the coating but also greatly depends on their respective ratios and on the particle size of the coated microparticle.

Therefore Bartholomaeus does not disclose microparticles meeting the structural requirements of the instant claims.

Therefore, independent claim 1 is patentable over Bartholomaeus. Dependant claims 2, 14, 15, 20 - 22 and 24 depend from independent claim 1. Dependent claims 2, 14, 15, 20 - 22 and 24 add further patentable features to the patentable features of independent claim 1.

Claims 1, 2, 14, 15, 20 - 22 and 24 are patentable over the cited reference. Withdrawal of the rejection and allowance of all claims are respectfully requested.

Rejections under 35 U.S.C. § 103

Claims 1 - 10, 13 - 22 and 24 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Santus et al. (U.S. Patent No. 5,405,619), hereafter "Santus".

Claims 7 and 8 have been canceled without prejudice. A such, claims 1 - 6, 9, 10, 13 - 22 and 24 are patentable over Santus. Withdrawal of the rejection and allowance of all claims are respectfully requested.

Independent claim 1, as amended, requires that the dosage form comprises "reservoir" microcapsules of active principle, each coated with one single coating film wherein the coating film comprises at least one hydrophilic polymer A carrying groups that are ionized at neutral pH, and at least one hydrophobic compound B". Support for the amendments may be found in the original specification, including the examples. Applicants respectfully submit that no new matter has been added by the amendments.

As such, the coating film must comprise both "at least one hydrophilic polymer A" and "at least one hydrophobic compound B".

Santus teaches granules with separate, successive coatings. See Santus at C. 5, ll. 4 - 22. "The film coating consists of a first layer deposited on the granulate, followed by a succession of one or more superimposed layer is 'onion-wise' [sic], consisting of lipophilic and hydrophilic suitably alternated materials." See Santus at C. 5, ll. 43 - 47.

In contrast, the claimed coating film is a mixture of hydrophilic compound A and hydrophobic compound B. See Specification at Examples. For instance, in Example 1 "93.3 g of hydrogenated palm oil (Hüls) (B) and 140 g of Eudragit® L100 (Röhm) (A) are dissolved in hot isopropanol B/A=0.66. The solution is sprayed onto 700 g of previously prepared microparticles." See Specification at Example 1. Therefore, both the hydrophilic polymer A and hydrophobic polymer B are applied in a single coating to the microcapsules of active principle.

Santus does not disclose that the coating film includes both hydrophilic polymer A and hydrophobic polymer B. Instead, Santus teaches separate, successive coatings.

A multilayer coating is intrinsically different from a monolayer coating and does not give the same results just because the same chemical ingredients are used. A polymer on its own will structure itself as a homogeneous film, with a given porosity. When admixed with a fatty component, it will organize itself differently, around crystalline waxy domains, yielding a

heterogeneous film with its own porosity, and hence a different permeability. If one could obtain the same results by superposing two layers a and b as by mixing their constituents, there would be no point in superposing, as Santus teaches, multiple layers, which is costly.

The Examiner states that the burden is upon the Applicant to prove that the claimed products are functionally different from those taught by Santus (see Office Action at page 14). However, the Applicant cannot compare the examples of Santus with the invention because those examples from Santus do not indicate either the amount of granules used or the amount of coating deposited, nor even the actual number of coatings. Therefore, it is not possible for anybody to reproduce effectively these products and verify their properties.

Santus not only does not have the structural requirements of the invention, but it does not teach a composite coating comprising A and B.

Therefore, independent claim 1 is patentable over Santus. Dependant claims 2 - 6, 9, 10, 13 - 22 and 24 depend from independent claim 1. Dependent claims 2 - 6, 9, 10, 13 - 22 and 24 add further patentable features to the patentable features of independent claim 1.

Claims 1 - 6, 9, 10, 13 - 22 and 24 are patentable over the cited reference. Withdrawal of the rejection and allowance of all claims are respectfully requested.

CONCLUSION

In view of the foregoing, it is respectfully submitted that the pending claims are in condition for allowance. Entry of this amendment and an early notice to this effect is earnestly solicited. Should there be any questions regarding this application, the Examiner is invited to contact the undersigned at the number shown below.

Applicants submit herewith a request for a one month extension of time and the corresponding fee. If additional fees are due, please charge our Deposit Account No. 50-2228, under Order Number 022290.0116C1US.

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Respectfully submitted,

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